Original Article

Survival and treatment of AIDS patients 1984–1993: experience of a smaller East London HIV centre

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Objective: To assess changes in survival from diagnosis of AIDS for patients managed in a small East London HIV clinic and the impact of therapeutic interventions on these survival patterns.
Design: Prospective observational study.
Setting: Grahame Hayton Unit, Royal London Hospital.
Subjects: 156 AIDS patients managed between 1984 and 1993.
Main outcome measure: Survival from diagnosis of AIDS.
Results: Median survival for those diagnosed with AIDS before 1 January 1987 was 9·4 months compared with 27·2 months after 1 January 1987 (logrank $\chi^2 = 10{\cdot}3$, $p = 0{\cdot}001$): CD4 count at time of AIDS and treatment with zidovudine or PCP prophylaxis were significantly associated with survival from time of AIDS. Of the 156 AIDS patients, 93 had been treated with zidovudine sometime during their follow up, 60 had received primary and 50 secondary *Pneumocystis carinii* pneumonia (PCP) prophylaxis. After controlling for gender, sexual orientation, age at time of AIDS, CD4 count at time of AIDS, diagnosis when first presenting to the clinic (AIDS/non-AIDS) and year of AIDS diagnosis, all patients who received either zidovudine or PCP prophylaxis had significant reductions in the risk of dying compared with those who received neither PCP prophylaxis nor zidovudine: a reduction in risk of dying between 71% (95%CI 40% to 86%) and 83% (95%CI 50% to 94%) was observed depending on the combination of zidovudine and PCP prophylaxis.
Conclusion: A debate is currently taking place about the format and value of HIV service provision with increasing numbers of HIV infected individuals managed at smaller HIV clinics. Larger clinics concentrate clinical expertise on a single site and facilitate clinical trials. Smaller well run HIV units staffed by competent health professionals not only provide clinical outcomes similar to those obtained in the larger centres, but may also allow a more informal and intimate setting for HIV infected individuals who want to be treated nearer their area of residence.
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Keywords: AIDS; survival; treatment; London

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Introduction

Information on survival of UK AIDS patients was initially described by the larger HIV clinics located in Central or West London,[1–3] reflecting the development of HIV services in these areas. As the HIV epidemic evolved, and genitourinary medicine services were improved as part of the national response to the HIV epidemic,[4] an increasing number of HIV infected individuals presented to local HIV services in East London which developed and expanded over time.

There is a current debate as to whether smaller HIV centres can deliver the same quality service as larger clinics, with a patient workload in excess of 1000 live patients. While survival patterns have recently been reported from smaller clinics outside London that are comparable with those from the larger London clinics,[5 6] other studies suggest that survival in patients reported from centres with a large known AIDS case-load tend to survive longer.[7] None of these analyses, however, adjusted survival for case-severity at time of diagnosis and therapy received.

Some data from the United States have suggested that larger centres had better survival patterns for patients with *Pneumocystis carinii* pneumonia (PCP) when compared with smaller clinics.[8–10] This was attributed to greater clinical proficiency of physicians working in "high volume" and "high experience" AIDS centres versus "low volume" and "low experience" AIDS centres.[10] This study aimed to investigate survival and treatment patterns for AIDS patients managed at a medium sized HIV clinic located in East London.

Methods

During the study period, 171 AIDS patients (out of a total 539 HIV infected individuals seen between 1 January 1984 and 31 December 1993) were managed at the Grahame Hayton Unit (GHU), the HIV clinic of the Royal London Hospital. Since HIV services were established in the GHU, a database was developed in 1991 which prospectively collected activity, clinical and behavioural data on all HIV infected individuals who attended.

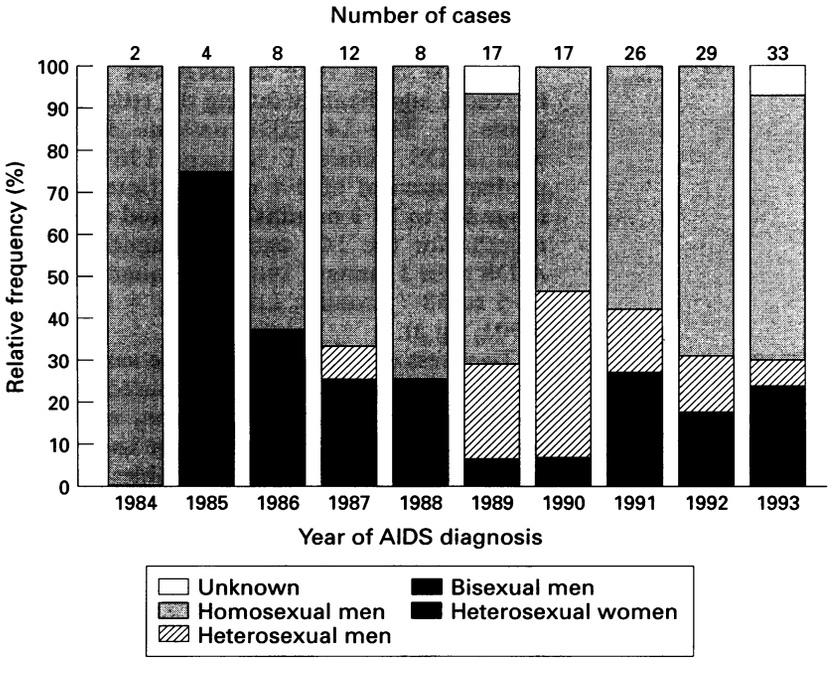

Figure 1 Number of AIDS patients by year of diagnosis and relative frequency of gender and sexual orientation.

Data before 1991 were obtained retrospectively from case notes.

All HIV infected patients were allocated to specific doctors to ensure continuity of medical care. Zidovudine was licensed in the UK in April 1987 and introduced into routine clinical practice in the GHU in December 1987, initially prescribed at the recommended oral dosage of 200 mg four hourly, which changed over time to either 250 mg twice daily or 200 mg three times-a-day. Routine prophylaxis against PCP was introduced in March 1988, initially consisting of 300 mg of nebulized pentamidine once a month. From 1990 onwards an increasing number of individuals were treated with other regimens, in particular daily oral co-trimoxazole (960 mg) or alternatively dapsone (100 mg) and pyrimethamine (25 mg) daily, three times per week.

AIDS diagnoses definitions used were the 1987 Communicable Disease Surveillance Centre (CDSC) diagnoses.[11-12] Dates of death were updated until 31/12/94, by seeking confirmation from the CDSC of any deaths of patients included in the study. Those, for whom no date of death was known, were presumed to have been lost to follow up and censored at last date known to have been alive. Of the 171 patients, 15 were part of clinical trials and as their treatments were still blinded, they were excluded from the analyses. Important missing data were obtained retrospectively from the case notes. All data were entered on dBase IV and subsequently transferred onto the Statistical Analysis System software package for analysis.[13] The Mann-Whitney test was used to make comparisons between groups, because of the skewed nature of some of the data. Survival patterns were analysed using Kaplan-Meier survival curves; the logrank statistic was used to test for statistical difference in survival times from AIDS to death for various patient groups. Cox's proportional hazards regression models with single explanatory variable were initially used to assess the risk of individual prognostic variables on the survival from diagnosis of AIDS for the various groups. A multivariable proportional hazards model was subsequently built, allowing the risk of particular prognostic variables to be assessed while controlling for the others in the model. The final multivariable Cox's proportional hazards regression model was tested for its distributional assumption using Cox-Snell residual plot and adjusted for year of AIDS diagnosis for its possible confounding effect.

Results

During the study period, the 156 AIDS patients who were not part of a particular clinical trial, comprised 91·2% of all AIDS patients. The overall AIDS caseload increased during the study period (fig 1). Women were significantly younger at time of AIDS diagnosis when compared with men (table 1). Of the 156 patients, 135 (86%) were Caucasians, 14 (9·0%) were Africans and five (3%) were of Afro-Caribbean origin; of the remaining two patients, one was Indian and one was of Pakistani origin. Sixteen (10%) were heterosexual women and of the 140 men, 98 (70%) were homosexual, 22 (16%) heterosexual and 17 (12%) were bisexual. Sexual orientation for the remaining three men was unknown. Nine

Table 1 Number of AIDS cases by gender, sexual orientation, year of AIDS diagnosis and mean age at AIDS diagnosis (years); median survival time from diagnosis of AIDS in months by year of AIDS diagnosis (including upper and lower quartile ranges)

a	*1984*	*1985*	*1986*	*1987*	*1988*	*1989*	*1990*	*1991*	*1992*	*1993*	*Total*
Cases	2	4	8	12	8	17	17	26	29	33	156
Survival from AIDS median (months)	19·1	7·6	9·3	34·5	32·1	25·4	29·5	26·6	27·5	21·3	Logrank $\chi^2 = 18·7$
inter-	9·0	3·6	6·0	7·8	15·2	19·0	13·8	19·2	10·6	4·4	$p = 0·03$
quartile	to	to	to	to	to	to	to	to	to	to	
range	29·2	13·6	26·9	77·0	82·2	63·8	53·7	44·2	35·1	*	

b		
Heterosexual	n	Age (95% CI)
women	16	29·2 (27·2 to 31·1)
Homosexual men	98	35·6 (34·0 to 37·2)
Heterosexual men	22	33·1 (30·4 to 35·8)
Bisexual men	17	33·7 (29·5 to 37·8)
Men unknown sexual orientation	3	42·1 (32·8 to 51·4)

*Upper quartile could not be calculated for this year because of censoring.

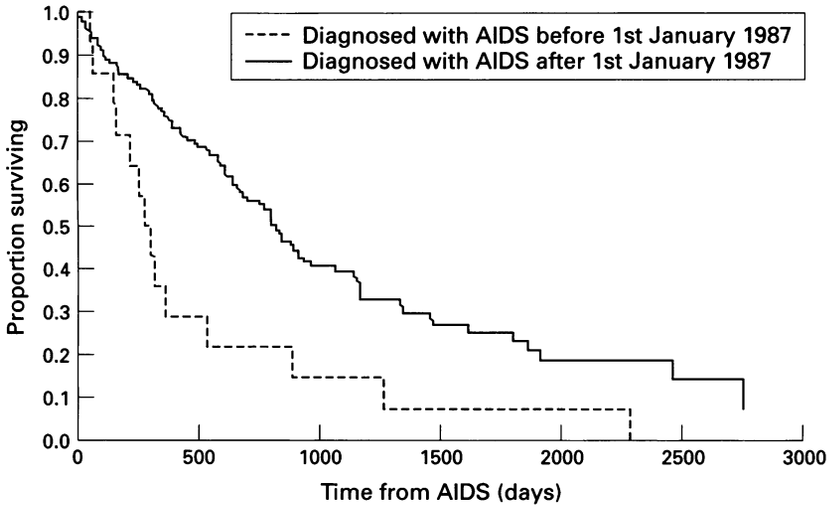

Figure 2 Survival time (days) from diagnosis of AIDS for patients diagnosed with AIDS before 1987 and since 1987.

individuals had an history of injecting drug use, all of whom were men: five heterosexuals, three homosexuals and one bisexual.

Of all patients, 91 (58%) first presented to the GHU with an AIDS defining diagnosis. No significant differences in terms of median CD4 counts at time of AIDS were, however, observed between those who presented with AIDS and those who did not (75 cells/mm^3 versus 100 cells/mm^3 respectively, Mann-Whitney p = 0·52). For neither group did the median CD4 count at diagnosis of AIDS change significantly during the study period.

Apart for treatment for specific opportunistic illnesses, 93 (60%) of all patients had received zidovudine at any time during the study period. Twenty one patients received zidovudine for a median of 181 days before being diagnosed with AIDS (range 45 to 639 days), while 90 received zidovudine for a median of 92 days since their diagnosis of AIDS (range 45 to 1369 days). Sixty patients (38%) had been on primary PCP prophylaxis, 50 (32%) on secondary PCP prophylaxis and 46 (29%) had never received primary or secondary PCP prophylaxis.

Survival from time of diagnosis of AIDS increased significantly during the study period (table 1). The 14 AIDS patients diagnosed with AIDS before 1 January 1987 had a median survival of 9·4 months (interquartile range 5·3 to 17·3 months) compared with 27·2 months for the 142 patients diagnosed with AIDS after 1 January 1987 (interquartile range 12·5 to 53·7 months; Logrank χ^2 = 10·8, p = 0·001, fig 2).

To assess the importance of the various factors which could have contributed to this improvement in survival patterns, univariate proportional hazards models were used in the first instance (table 2). The variables assessed included gender, sexual orientation, age at diagnosis of AIDS, whether or not patients presented with AIDS at first visit, CD4 count at time of AIDS and treatment with zidovudine or PCP prophylaxis during the study period: CD4 count at time of AIDS, treatment with zidovudine or PCP prophylaxis (primary or secondary) were statistically significantly associated with survival (table 2). Those diagnosed with a CD4 count at the time of AIDS diagnosis of greater than 500 cells/mm^3 had a reduction in their risk of dying of 83% (95%, CI 22% to 92%) compared with patients presenting with a CD4 count of less than 200 cells/mm^3 (table 2). Similarly, all patients who received either zidovudine or PCP prophylaxis had significant reductions in the risk of dying compared with those who received neither PCP prophylaxis nor zidovudine (table 2).

Survival patterns from diagnosis of AIDS for patients who received zidovudine or PCP prophylaxis were compared with those who never received zidovudine or PCP prophylaxis. For patients who received either zidovudine or PCP prophylaxis, survival was significantly better when compared with those who received neither zidovudine nor PCP prophylaxis (Logrank χ^2 = 23·3, p = 0·0003; fig 3). The effect of different treatment combinations

Table 2 Univariate hazards models for individual variables and multivariate proportional hazards model adjusted for displayed variables; survival from time of AIDS diagnosis was dependent variable for both univariate and multivariate models (n = 156)

		Total	Died (%)	Likelihood ratio statistics	Unadjusted hazard ratio (95% CI)	Likelihood ratio statistics	Adjusted hazard* ratio (95% CI)
Unknown sexual orientation		3	1 (33·3)	6·06,	0·45 (0·06 to 3·24)		0·26 (0·03 to 2·26)
Heterosexual women		16	11 (68·8)	Df = 4,	1·14 (0·60 to 2·16)		0·99 (0·48 to 2·02)
Bisexual men		17	14 (82·4)	p > 0·05	1·60 (0·89 to 2·87)		1·06 (0·52 to 2·18)
Heterosexual men		22	13 (59·1)		0·66 (0·36 to 1·20)		1·49 (0·75 to 2·96)
Homosexual men		98	65 (66·3)		1·0		1·0
Age at time AIDS†		156	104 (66·7)	0·47, Df = 1, p > 0·05	0·99 (0·97 to 1·02)		1·00 (0·97 to 1·03)
AIDS at presentation to GHU	yes	91	63 (69·2)	0·25, Df = 1, p > 0·05	0·91 (0·61 to 1·34)	0·18, Df = 1, p > 0·05	1·11 (0·68 to 1·82)
	no	65	41 (63·1)		1·00		1·00
CD4 count at AIDS diagnosis	not known	31	25 (80·7)	16·02, Df = 3, p < 0·05	1·72 (1·07 to 2·74)	17·30 Df = 3, p < 0·05	1·06 (0·56 to 2·00)
	> 499	8	3 (37·5)		0·27 (0·08 to 0·88)		0·15 (0·04 to 0·52)
	200–499	28	15 (53·6)		0·65 (0·37 to 1·16)		0·46 (0·23 to 0·93)
	< 200	89	61 (68·5)		1·00		1·00
Sec PCP & Zidovudine		37	28 (75·7)	18·67 Df = 5, p < 0·05	0·44 (0·25 to 0·76)	20·40, Df = 5 p < 0·05	0·29 (0·14 to 0·60)
Sec PCP‖ & No Zidovudine		13	5 (38·5)		0·29 (0·11 to 0·77)		0·17 (0·06 to 0·50)
Prim PCP & Zidovudine		45	29 (64·4)		0·32 (0·18 to 0·55)		0·21 (0·10 to 0·46)
Prim PCP§ & No Zidovudine		15	8 (53·3)		0·45 (0·20 to 1·01)		0·19 (0·07 to 0·52)
No PCP & Zidovudine		15	9 (60·0)		0·28 (0·13 to 0·62)		0·19 (0·07 to 0·51)
No PCP‡ & No Zidovudine		31	25 (80·7)		1·00		1·00

Key: *adjusted for all other factors in the model and year of AIDS diagnosis; †continuous variable, hazard ratio change per year increase in age; ‡No PCP = no PCP prophylaxis, neither primary nor secondary; §Prim PCP = primary PCP prophylaxis; ‖Sec PCP = secondary PCP prophylaxis.

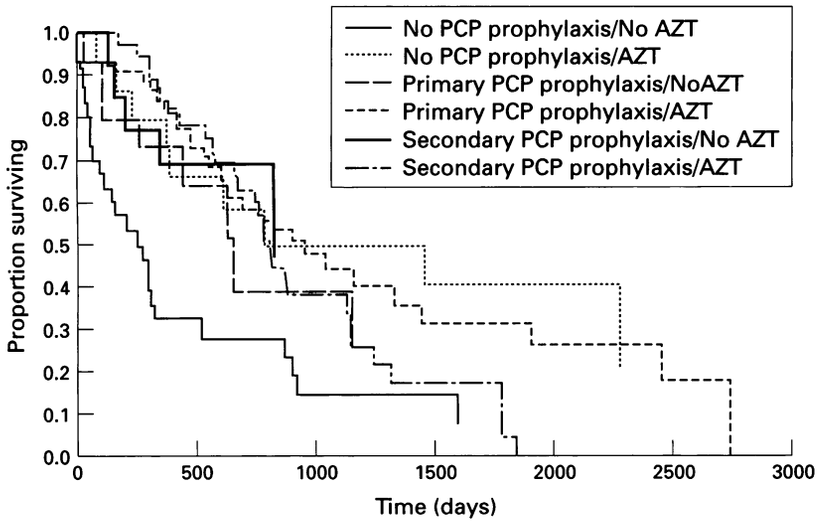

Figure 3 Survival time (days) from diagnosis of AIDS for patients with different treatment regimens during the study period.

with zidovudine or PCP prophylaxis was further investigated using a multivariate proportional hazards model controlling for gender, sexual orientation, age at time of AIDS, CD4 count at time of AIDS, diagnosis when first presented to the GHU (AIDS or non-AIDS) and year of AIDS diagnosis. All patients who received either zidovudine or PCP prophylaxis had significant reductions in the risk of dying—ranging from 71% (95%, CI 40% to 86%) to 83% (95%, CI 50% to 94%)—when compared with those who received neither PCP prophylaxis nor zidovudine (table 2).

Discussion

Over the study period there was a sustained increase in the number of AIDS patients attending the GHU. This was partly due to a small net transfer of patients from the larger West or Central London centres to centres closer to home. Some locally resident patients with advanced disease deliberately chose to transfer their care to the GHU, thus reducing distances they needed to travel. In contrast, a few patients elected to transfer their care from the GHU to larger centres, enabling them to have access to a wider range of investigational drugs. However, the largest contribution to the rise in numbers of patients attending came from an increasing number of HIV infected individuals presenting directly to the GHU. The proportion of heterosexual and non-Caucasian AIDS patients was higher than those recently reported from St. Mary's Hospital in West London,[14] although survival patterns did not differ significantly between men and women, nor between men of different sexual orientation.

Not only are the survival patterns from diagnosis of AIDS in the GHU similar to those observed in larger clinics, significant improvements over time also resemble those observed in the larger clinics.[1,2] Similarly, the modest reduction in median survival after 1988 at the GHU has also been observed in larger clinics[14] and at a national level (PA Rogers, personal communication 1996). This could be due to the increased use of primary PCP prophylaxis, resulting in fewer patients presenting with PCP as their first AIDS defining diagnosis and thereby reducing the AIDS-to-death time interval. Our findings suggest that survival from diagnosis of AIDS cannot be used as a criterion to argue that individuals with HIV infection should be solely managed in larger specialist centres with the requisite expertise and concentration of resources as is currently being suggested.[15]

Survival of individuals with symptomatic HIV disease is dependent on both effective anti-retroviral treatment combined with the treatment of opportunistic illnesses.[16] The significant increase in survival which occurred for AIDS patients diagnosed before 1 January 1987 compared with those diagnosed after that date may be related to the introduction into routine clinical practice of zidovudine in 1987 or PCP prophylaxis in 1988. While some consider PCP prophylaxis to have been more important in improving survival from time of AIDS,[17] other data suggest a similar influence for zidovudine.[18] It was therefore of considerable interest to find that in our sample the risk of dying was similarly reduced for different combinations of use of zidovudine or PCP prophylaxis compared with individuals who received neither zidovudine nor PCP prophylaxis.

The value of medical intervention in HIV infection has recently been questioned.[14] This particular study only analysed survival patterns for AIDS patients diagnosed between 1991 and 1993, failing to acknowledge the improvement in survival which had occurred at the same hospital since 1987.[1,2] Furthermore, survival analyses were neither adjusted for case-severity or case-mix,[19–21] nor for treatment received since diagnosis of AIDS. Our data suggest that both zidovudine and PCP prophylaxis have played important roles in improving survival from time of AIDS, in addition to earlier diagnosis of HIV infection,[22,23] (resulting in AIDS patients being diagnosed with less severe opportunistic illnesses[23]) as well as improved clinical expertise.[24] The importance of increasing hospital experience on survival has recently been confirmed (PA Rogers, personal communication 1996) as has the importance of clinical experience of individual clinicians.[25]

While subsequent service and therapeutic developments have not improved survival patterns since the early 1990s—something which is likely to change with the introduction of combination anti-retroviral therapy[26–29]—these developments may well have contributed to improved quality of life of patients with HIV disease. Thus, well run smaller HIV units staffed by competent health professionals may not only provide clinical outcomes similar to those obtained in the larger centres, but may provide a more informal and friendly setting for HIV infected individuals who want to be treated nearer their area of residence. Having to travel long distances for treatment may have a detrimental effect on the quality of life of patients, especially for those with end stage HIV disease.

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